Impact of tumor infiltrating lymphocytes (TILs) on local progression-free (LPFS) and disease-free (DFS) survival in localized high-risk soft tissue sarcoma (HR-STS) after neo-adjuvant chemotherapy (NAC) with regional hyperthermia (RHT)

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Aim: Clinical results showed significant improvement of LPFS and DFS by adding RHT to NAC (Issels et al. Lancet Oncol 2010). Here, we investigated the hypothesis whether TILs in STS biopsies predict treatment outcome in this study.

Methods: The EORTC 62961-ESHO phase 3 study investigated 341 patients (pts) with HR-STS (grade 2/3, > 5 cm) comparing NAC with the combination (NAC + RHT).

From 109 randomized pts (53 NAC, 56 NAC + RHT), 137 paraffin-embedded core biopsies were available before (84) or after (53) NAC ± RHT treatment. TILs were assessed by counting in standard HE stained tissue microarrays (TMA). IHC staining was performed for CD3, FOXP3 and PD-1. TILs were defined to be high (> 5 TILs/TMA) or low (≤ 5 TILs/TMA). Outcome was compared using Kaplan Meier and Cox estimations. IRB approval and written informed consent were obtained.

Results: In 84 initial biopsies, TILs were high in 17/84 (20.2%) and low in 67/84 (79.8%). By comparison, in the 53 post-treatment biopsies the high TILs fraction was increased and the proportion equally balanced: TILs high in 26/53 (49.1%) and low in 27/53 (50.9%). PD-1+ infiltration did not change, whereas FOXP3+ (T-reg cells) were reduced after treatment. CD3 was 60-80% expressed in TILs. Analyzing initial biopsies, survival outcome for high- vs low-TILs pts was not different (LPFS: HR 1.07; n.s.; DFS: HR 1.14, n.s.) whereas after treatment the results were independent of grade significantly in favor of high-TILs pts (LPFS: HR 0.46, 95% CI: 0.23 - 0.96; log-rank p = 0.0325; DFS: HR 0.49, 95% CI: 0.24 - 0.98; log-rank p = 0.040). The % of high TILs in initial vs post-treatment biopsies after NAC + RHT increased nearly four-fold (15.8% to 58.1%) whereas this was not seen after NAC alone (23.9% to 36.4%).

Conclusions: We report first indication in soft-tissue sarcoma that high TILs in response to therapy may be predictive for local control and survival. The effect of regional hyperthermia to increase the fraction of high TILs in tumor tissue and the depletion of negative regulatory T cells by chemotherapy suggest a new immune therapeutic potential for the combined application.

Clinical trial identification: NCT 00003052

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